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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/585,475	06/02/2000	N. Leigh Anderson	40488	6582

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EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	10

DATE MAILED: 09/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/585,475	ANDERSON ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,10-13 and 85-95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 10-13 and 85-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: copies of papers used in 103 rejection.

The Amendment under 37 CFR § 1.111 filed on June 21, 2002 as paper No. 9 as acknowledged. The amendments to the title, specification and claims have been entered as requested. Claims 7-9 are cancelled. Claims 1, 4-5, 10-13 are amended. New claims 85-95 are added. Claims 1-6, 10-13 and 85-95 are pending in the application and are the subject of this Office Action.

Office Action

1. Objections

1.1. Specification

The objection to the title and specification have been withdrawn in the light of the amendment and Applicants' arguments.

3.1. Claims

Objections to claims 5, 10 and 12 are withdrawn in the light of amendments and Applicants' arguments.

3. Rejections

3.1. 35 USC, section 112, second paragraph

Claims 1-6, 10-13 and 95 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are directed to a method for determining a degree of efficacy of an agent, however neither the claims nor the specification define the term efficacy. It is unknown to what the word efficacy is related. Is this an efficacy of a drug in the treatment of a particular disorder? How the degree of efficacy is defined? The indefinite term and phrase render the claims indefinite.

The claims are also indefinite in the recitation of "an agent candidate not previously known to have toxicity or efficacy". The scope of what is "not known" changes with time, as it is impossible to define even at a single point in time all that is "not known" and even if that were feasible the specification does not define what characteristics must have been shown not to be present in an agent for it to be included within the class of "known to have toxicity or efficacy", i.e., positive results in some assay, a disclosure that a compound has such properties without any supporting data, or even merely some suggestion in the art that a compound might have such activity. As such the metes and bounds of this limitation cannot be defined and the claims are indefinite. For examination purposes it is assumed that the phrase means "an agent not previously tested".

In order to examine claim 1, it is assumed that the efficacy of an agent is any change it causes in the kind and content (concentration in the tissue) of the proteins isolated from the exposed tissue as compared to unexposed tissue or the same tissue exposed to an agent for which said changes are already known.

Claim 94 is confusing. It is not quite clear whether the agent recited by the claim is "a said known effective agent " recited by claim 93, or "an agent candidate not previously known to have toxicity of efficacy" recited by claim 1, or both.

The examiner suggests transfer of limitations of claim 92 into the base claim 85. Claims 1 and 95 are also suggested be amended to recite the control that is a biological sample containing protein from the same tissue of interest before the tissue is exposed to the tested agent.

3.2. *35 USC section 112, first paragraph – new rejection*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1-6, 10-13, and 85-95 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The specification fails to describe a degree of toxicity and/or efficacy and its measurements. The disclosure is enabling for determining changes in the presence and/or level of markers in a proteome, wherein the changes are caused by exposure of a tissue to tested chemicals. On page 6, line 26 the Applicants write: "Sets of

perturbed protein markers provide a proteomic pattern or 'signature' **INDICATING** [emphasis MW] relative toxicity and/or efficacy." Indicating does not mean quantifying a degree. The quoted passage means qualitative assay. Examples presented by Applicant are also silent about how to perform measurements of toxicity and efficacy. Thus, the disclosure is not enabling for a quantitative assay of toxicity/efficacy. Applicants do not teach any calibration curve that would represent a relationship between toxic effects measured by, for example, increased blood transaminases (see page 15, line 9) and changes in the level of particular marker/markers in the proteome. The discolsure also fails to teach any calibration curve for efficacy of a drug, as for example a relationship between the level of choresterol in the blood after treatment with a particular drug and a level of particular marker/markers in the proteome. In addition, the claimed subject matter is broad and includes unpredictable changes in the levels of proteins in the cell in response to the exposure to a drug or toxic agent. The quantity of some proteins may change in linear fashion; the amount of some proteins may be unaffected; some may disappear completely; some may change only after exposure to a certain threshold level of agent or may change in non-linear fashion. As such it would require undue experimentation to use any one or more protein markers to determine the efficiency or toxicity of a candidate agent absent guidance regarding how each marker changes in response to such agents and how the change correlate to toxicity and /or efficacy.

A skilled artisan concludes, therefore, the claimed subject matter was not described in the specification in such full, clear, concise and exact terms as to enable any person skilled in the art, to which it pertains, to use the invention.

3.3. 35 USC section 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1-13 and claim 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over the method of Anderson at al (A two-dimensional gel database of rat liver proteins useful in gene regulation and drug effects studies, *Electrophoresis*, **1991**, 12, 907-903, and further in view of current knowledge in toxicology, see for example review by Page M. J. et al. (Proteomics: a major new technology for the drug discovery process, *DDT*, February 2**, 1999**, 4, 55-62.)

Anderson and her co-workers exposed liver tissue in rats to antilipemic agents lovostatin, or lovostatin in combination with cholestyramine, or to none of the chemicals. The animals were sacrificed and livers removed, proteins extracted, and measurements of the levels of protein markers (MSN 413, 993, 1001, 1119, 1250 and 1253 – see Fig.10 and 11 on page 921) was performed in the liver proteome using

two-dimensional electrophoresis. In addition, changes in the levels of such markers as 119, 34, 79, 178, 182, 204, 537, 235, 134, and 144 were observed (page 912, line 2, 9, and 26). The change in the level of some markers may be assessed as statistically significant at $p < 0.01$ or $p < 0.001$. For example, the abundance of MSN 413 and MSN 1001 (Fig. 10 and 11 on page 921).

The claimed invention comprises testing agents of unknown toxicity or efficacy using display of proteome by two dimensional electrophoresis and measurements of levels of protein markers, wherein alternatively two control sample might be involved One of the controls is from the same tissue not treated with any agent, the other from the same tissue exposed to an agent of known toxicity or efficacy.

Anderson and her co-workers do not use as a control sample protein form the tissue exposed to compounds with known toxicity and efficacy, neither they use agents not tested previously, because lovostatin and cholestyramine were commonly used drugs at the time of Anderson and al.'s measurements. However, summarizing their application of the proteome visualization to studies in toxicology, they state on page 912, line 29: "Its practical utility in several areas of mechanistic toxicology is already been demonstrated."

Page et al. in the first sentence of the abstract indicate: "Proteomics is a new enabling technology that is being integrated in to the drug discovery process." It is therefore obvious that the technology disclosed by Anderson is used to test "agent candidates not previously known to have toxicity or efficacy ". Page et al. address the

use of the technology for toxicity and pharmacokinetic investigation of new drugs on page 61 in the section *Use of proteomics in formal drug toxicology studies*.

It would have been obvious to one having ordinary skill in the art at the time of invention to have the method described by Anderson and her coworkers and apply to testing new compounds of unknown toxicity and efficacy as drugs, as suggested by Anderson and commonly practiced in drug discovery process; see reviewed by Page at al. It would also have been obvious, if necessary, to use as a control the proteome from a tissue treated with an agent considered to be a standard in particular screening.

The motivation would be to have a method of screening for toxic and pharmacologic effects of potentially new drugs, wherein the said method would give additionally a comparison of effects of new compounds with that of the already known.

The expectation of success is very high, because exposure of a tissue to a chemical results always in some impairment of protein expression, synthesis and metabolism, and these changes are manifested by changes in the presence and/or level, of toxicity and/or efficacy markers in the proteome of exposed tissues.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Claims 85-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over the method of Anderson at al (A two-dimensional gel database of rat liver proteins useful in gene regulation and drug effects studies, *Electrophoresis*, **1991**, 12, 907-903).

Anderson and her co-workers exposed liver tissue in rats to antilipemic agents lovostatin, or lovostatin in combination with cholestyramine, or to none of the chemicals. The animals were sacrificed and livers removed, proteins extracted, and the levels of the following from thousands of protein markers (MSN 413, 993, 1001, 1119, 1250 and 1253 – see Fig.10 and 11 on page 921) were measured in the liver proteome using two-dimensional electrophoresis. In addition changes in the levels of such markers as 119, 34, 79, 178, 182, 204, 537, 235, 134, and 144 was observed (page 912, line 2, 9, and 26). The change in the level of some markers may be assessed as statistically significant at $p < 0.01$ or $p< 0.001$. For example, the abundance of MSN 413 and MSN 1001 (Fig. 10 and 11 on page 921).

The claimed invention comprises testing an agent using display of proteome by two dimensional electrophoresis and measurements of levels of protein markers other than MSN 34, 79, 182, 204, 347, 413, 633, 933, 101 and 1250, wherein alternatively two control sample might be used. One of the controls is from the same tissue not treated with any agent, the other from the same tissue exposed to an agent of known toxicity or efficacy.

Anderson at al. do not teach using alternatively two control samples, but they use, as mentioned above, markers displayed in the gel that are other than MSN 34, 79, 182, 204, 347, 413, 633, 933, 101 and 1250; for example markers with MSN 119, 537 or 144.

It would have been obvious to one having ordinary skill in the art at the time of invention to have the method described by Anderson and her coworkers and if

necessary, apply as a control not only the proteome from unexposed tissue, but also from a tissue treated with an agent considered to be a standard in particular screening. It is a routine in the art to compare effects of two drugs.

The motivation would be to have a method of screening for toxic and pharmacologic effects of potentially new drugs, wherein the said method in addition to indicate potential toxicity and efficacy would enable comparison of the tested drug with already known drugs.

The expectation of success is very high, because exposure of a tissue to a chemical always result in some changes in protein expression, synthesis and metabolism, and these changes are manifested by changes in the presence and/or level, of toxicity and/or efficacy markers.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

4. Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.
Art Unit 1652
Patent Examiner

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PRIMARY EXAMINER
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